NDA 21-065/S-004

JUL 14 2000

Parke-Davis
Attention: Sharon Phillips
Senior Manager, Advertising and Labeling Worldwide Regulatory Affairs
201 Tabor Road
Morris Plains, New Jersey 07950

Dear Ms. Phillips:

Please refer to your supplemental new drug application dated March 2, 2000, received March 3, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for femhrtTM, (norethindrone acetate and ethinyl estradiol) tablets, 1 mg/5mcg daily

We acknowledge receipt of your submission dated May 26, 2000.

This "Changes Being Effected" supplemental new drug application proposes the following changes:

1. Revise the CLINICAL PHARMACOLOGY, Clinical studies, Effects on Vasomotor Symptoms subsection, to clarify the number of patients in this study as well as the number of patients in each treatment group.

2. Revise Table 4 in the ADVERSE REACTIONS section, to eliminate those adverse events that occurred at a frequency less than 5%.

3. Change TM to ® and adding the Copyright.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

In the DESCRIPTION section of the Package insert

1. The chemical name for Norethindrone acetate,

   "[(17-alpha)- 17-(acetyloxy)- 19-norpregna-4-en-20-yn-3-one]"

should be replaced with:

   "[19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17%)-]"

2. The chemical name for Ethinyl estradiol stated as,

   "[(17-alpha)- 1 9-norpregna- 1,3,5(1 0)-trien-20-yn-2, 17-diol]"

should be replaced with:

   "[19-Norpregna- 1,3,5(1 0)-trien-20-yne-3, 1 7-diol, (17%)-]"

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted March 2, 2000, patient package insert submitted March 2, 2000). These revisions are terms of the approval of this application.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 2 1-065/S-004." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i:e., a “Dear Health Care Practitioner” letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Dornette Spell-LeSane, NP-C, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Susan Allen, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

f e m h r t®

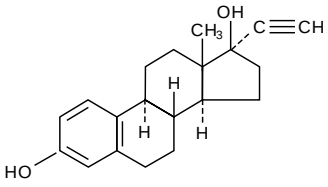
(norethindrone acetate/ethinyl estradiol tablets)

DESCRIPTION

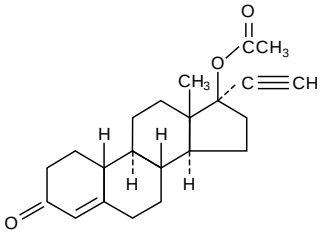
femhrt® 1/5 is a continuous dosage regimen of a progestin-estrogen combination for oral administration.

Each white D-shaped tablet contains 1 **mg** norethindrone acetate [(17-alpha)-17-(acetyloxy)-19-norpregna-4-en-20-yn-3-one] and 5 **mcg** ethinyl estradiol [(17-alpha)-19-norpregna-1,3,5(10)-trien-20-yn-2, 17-diol]. Each tablet also contains calcium stearate, lactose monohydrate, microcrystalline cellulose, and cornstarch.

The structural formulas are as follows:



Ethinyl Estradiol
Molecular Weight: 296.41
Molecular Formula: $C_{20}H_{24}O_2$



Norethindrone Acetate
Molecular Weight: 340.47
Molecular Formula: $C_{22}H_{28}O_3$

CLINICAL PHARMACOLOGY

Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sex characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone and estriol at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulphate conjugated form, estrone sulphate, are the most abundant circulating estrogens in postmenopausal women. The pharmacologic effects of ethinyl estradiol are similar to those of endogenous estrogens.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

Progestin compounds enhance cellular differentiation and generally oppose the actions of estrogens by decreasing estrogen receptor levels, increasing local metabolism of estrogens to less active metabolites, or inducing gene products that blunt cellular responses to estrogen. Progestins exert their effects in target cells by binding to specific progesterone receptors that interact with progesterone response elements in target genes. Progesterone receptors have been identified in the female reproductive tract, breast, pituitary, hypothalamus, bone, skeletal tissue and central nervous system. Progestins produce similar endometrial changes to those of the naturally occurring hormone progesterone.

The use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma. The addition of continuous administration of progestin to an estrogen replacement regimen reduced the incidence of endometrial hyperplasia, and the attendant risk of carcinoma in women with intact uteri.

Pharmacokinetics

Absorption and Bioavailability

Norethindrone acetate (NA) is completely and rapidly deacetylated to norethindrone after oral administration, and the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone. Norethindrone acetate and ethinyl estradiol (EE) are rapidly absorbed from *femhrt* 1/5 tablets, with maximum plasma concentrations of norethindrone and ethinyl estradiol generally occurring 1 to 2 hours postdose. Both are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64% for norethindrone and 55% for ethinyl estradiol. Bioavailability of *femhrt* 1/5 tablets is similar to that from solution for norethindrone and slightly less for ethinyl estradiol. Administration of norethindrone acetate/ethinyl estradiol (NA/EE) tablets with a high fat meal decreases rate but not extent of ethinyl estradiol absorption. The extent of norethindrone absorption is increased by 27% following administration of NA/EE tablets with food.

The full pharmacokinetic profile of *femhrt* 1/5 (1 **mg** norethindrone acetate/5 **mcg** ethinyl estradiol) was not characterized due to assay sensitivity limitations. However, the multiple-dose pharmacokinetics were studied at a dose of 1 **mg** NA/10 **mcg** EE in 18 postmenopausal women. Mean plasma concentrations are shown below (Figure 1) and pharmacokinetic parameters are found in Table 1. Based on a population pharmacokinetic analysis, mean steady-state concentrations of norethindrone for 1 **mg** NA/5 **mcg** EE and 1/10 are slightly more than proportional to dose when compared to 0.5 **mg** NA/2.5 **mcg** EE tablets. It can be explained by higher sex hormone binding globulin (SHBG) concentrations. Mean steady-state plasma concentrations of ethinyl estradiol for the 0.5 **mg** NA/2.5 **mcg** EE tablets and *femhrt* 1/5 tablets are proportional to dose, but there is a less than proportional increase in steady-state concentrations for the NA/EE 1/10 tablet.

FIGURE 1. **Mean Steady-State (Day 87) Plasma Norethindrone and Ethinyl Estradiol Concentrations Following Continuous Oral Administration of 1 mg NA/10 mcg EE Tablets**

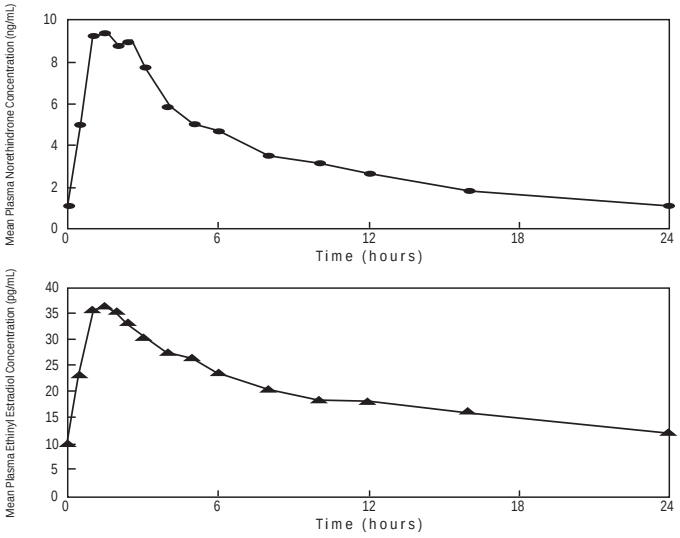


TABLE 1. Mean (SD) Single-Dose (Day 1) and Steady-State (Day 87) Pharmacokinetic Parameters[a] Following Administration of 1 mg NA/10 mcg EE Tablets

	C_{max}	t_{max}	AUC(0-24)	CL/F	$t_{1/2}$
Norethindrone	ng/mL	hr	ng•hr/mL	mL/min	hr
Day 1	6.0 (3.3)	1.8 (0.8)	29.7 (16.5)	588 (416)	10.3 (3.7)
Day 87	10.7 (3.6)	1.8 (0.8)	81.8 (36.7)	226 (139)	13.3 (4.5)
Ethinyl Estradiol	pg/mL	hr	pg•hr/mL	mL/min	hr
Day 1	33.5 (13.7)	2.2 (1.0)	339 (113)	ND[b]	ND[b]
Day 87	38.3 (11.9)	1.8 (0.7)	471 (132)	383 (119)	23.9 (7.1)

[a] C_{max} = Maximum plasma concentration; t_{max} = time of C_{max}; AUC(0-24) = Area under the plasma concentration-time curve over the dosing interval; CL/F = Apparent oral clearance; $t_{1/2}$ = Elimination half-life

[b] ND = Not determined

Based on a population pharmacokinetic analysis, average steady-state concentrations (Css) of norethindrone and ethinyl estradiol for *femhrt* 1/5 (1 **mg** NA/5 **mcg** EE) are estimated to be 2.6 ng/mL and 11.4 pg/mL, respectively.

The pharmacokinetics of ethinyl estradiol and norethindrone acetate were not affected by age, (age range 40-62 years), in the postmenopausal population studied.

Distribution

Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg. Plasma protein binding of both steroids is extensive (>95%); norethindrone binds to both albumin and sex hormone binding globulin (SHBG), whereas ethinyl estradiol binds only to albumin. Although ethinyl estradiol does not bind to SHBG, it induces SHBG synthesis.

Metabolism

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites. A small amount of norethindrone acetate is metabolically converted to ethinyl estradiol, such that exposure to ethinyl estradiol following administration of 1 **mg** of norethindrone acetate is equivalent to oral administration of 2.8 **mcg** ethinyl estradiol. Ethinyl estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa. Ethinyl estradiol may undergo enterohepatic circulation.

Excretion

Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites. Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/hr/kg). Steady-state elimination half-lives of norethindrone and ethinyl estradiol following administration of 1 **mg** NA/10 **mcg** EE tablets are approximately 13 hours and 24 hours, respectively.

Special Populations

Pediatric

femhrt 1/5 is not indicated in children.

Geriatrics

The pharmacokinetics of *femhrt* 1/5 have not been studied in a geriatric population.

Race

The effect of race on the pharmacokinetics of *femhrt* 1/5 has not been studied.

Patients with Renal Insufficiency

The effect of renal disease on the disposition of *femhrt* 1/5 has not been evaluated. In pre-menopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma ethinyl estradiol concentrations were higher and norethindrone concentrations were unchanged compared to concentrations in premenopausal women with normal renal function (see **PRECAUTIONS, Fluid Retention**).

Patients With Hepatic Impairment

The effect of hepatic disease on the disposition of *femhrt* 1/5 has not been evaluated. However, ethinyl estradiol and norethindrone may be poorly metabolized in patients with impaired liver function (see **PRECAUTIONS**).

Drug Interactions

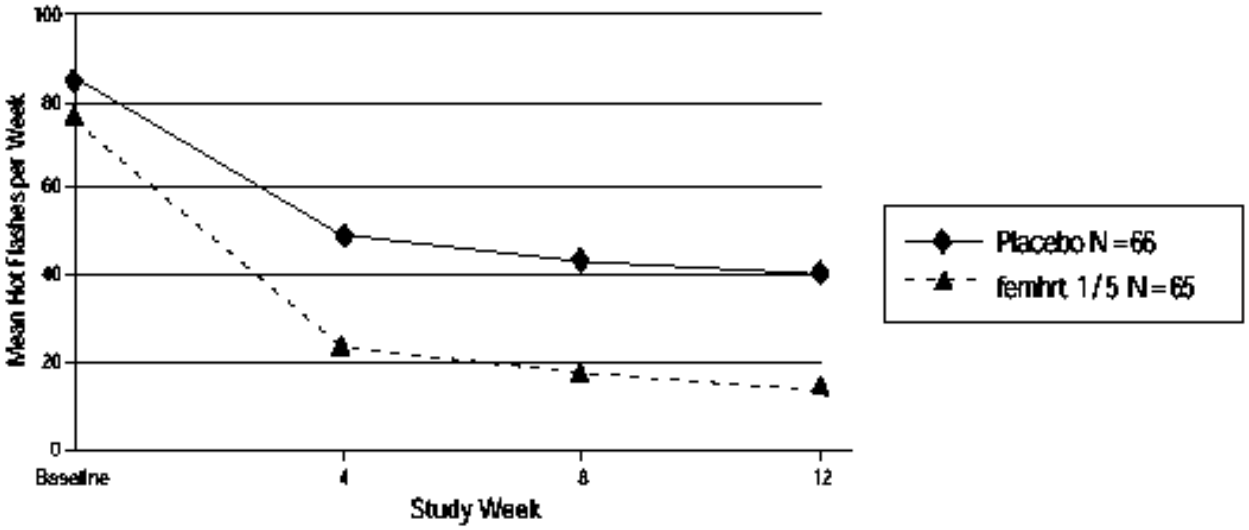
See **PRECAUTIONS, Drug Interactions**. **Clinical**

Studies Effects on Vasomotor Symptoms

A 12-week placebo-controlled, multicenter, randomized clinical trial was conducted to determine the safety and efficacy of *femhrt* 1/5 for the treatment of vasomotor symptoms. The study assessed the efficacy of *femhrt* 1/5 in 266 symptomatic women who had at least 56 moderate to severe hot flashes during the week prior to randomization. On average, these patients had 12 hot flashes per day upon study entry.

A total of 65 women were randomized to receive *femhrt* 1/5 and 66 women were radomized to the placebo group. The efficacy of *femhrt* 1/5 for the treatment of moderate to severe vasomotor symptoms (VMS) is demonstrated in Figure 2.

FIGURE 2. Mean Hot Flash Frequencies by Treatment Group: Baseline Through Week 12 (Intent-to-Treat Population, Last Observation Carried Forward)



Endometrial Hyperplasia

A 2-year, placebo-controlled, multicenter, randomized clinical trial was conducted to determine the safety and efficacy of *femhrt* 1/5 on maintaining bone mineral density, protecting the endometrium, and to determine effects on lipids. A total of 1265 women were enrolled and randomized to either placebo, 0.2 **mg** NA/1 **mcg** EE, 0.5 **mg** NA/2.5 **mcg** EE, *femhrt* 1/5 and 1 **mg** NA/10 **mcg** EE or matching unopposed EE doses (1, 2.5, 5, or 10 **mcg**) for a total of 9 treatment groups. All participants received 1000 mg of calcium supplementation daily. Of the 1265 women randomized

to the various treatment arms of this study, 137 were randomized to placebo, 146 to *femhrt* 1/5, and 141 to EE 5 **mcg**. Of these, 134 placebo, 143 *femhrt* 1/5, and 139 EE 5 **mcg** had a baseline endometrial result. Baseline biopsies were classified as normal (in approximately 95% of subjects), or insufficient tissue (in approximately 5% of subjects). Follow-up biopsies were obtained in approximately 70-80% of patients in each arm after 12 and 24 months of therapy. Results are shown in Table 2.

TABLE 2. Endometrial Biopsy Results After 12 and 24 Months of Treatment

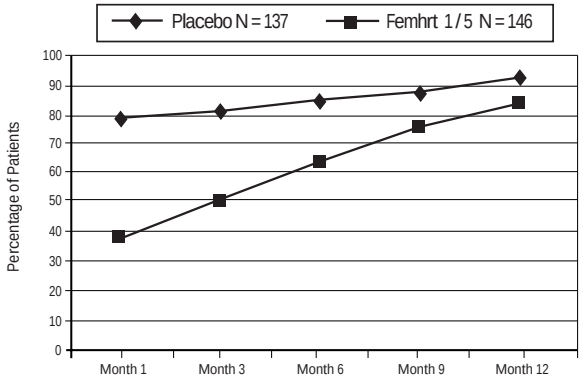
Number of Patients Biopsied at Baseline	Placebo N = 134	*femhrt* 1/5 N=143	5 mcg ethinyl estradiol N=139
MONTH 12			
Patients Biopsied (%)	113 (84)	110 (77)	114 (82)
Insufficient Tissue	30	45	20
Atrophic Tissue	60	41	2
Proliferative Tissue	23	24	91
Endometrial Hyperplasia[a]	0	0	1
MONTH 24			
Patients Biopsied (%)	94 (70)	102 (71)	107 (77)
Insufficient Tissue	35	37	17
Atrophic Tissue	38	33	2
Proliferative Tissue	20	32	86
Endometrial Hyperplasia[a]	1	0	2

[a] All patients with endometrial hyperplasia were carried forward for all time points.

Irregular Bleeding/Spotting

The cumulative incidence of amenorrhea, defined as no bleeding or spotting, was evaluated over 12 months for *femhrt* 1/5 and placebo arms. Results are shown in Figure 3.

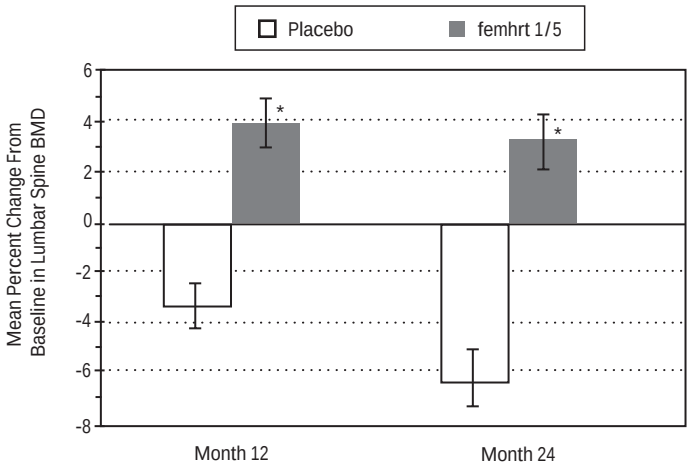
FIGURE 3. Patients With Cumulative Amenorrhea Over Time: Intent-to-Treat Population, Last Observation Carried Forward



Effect on Bone Mineral Density

In the 2 year study, trabecular bone mineral density (BMD) was assessed at lumbar spine using quantitative computed tomography. A total of 283 postmenopausal women with intact uteri and normal baseline bone mineral density (124.14 mg/cc ± 9.60 mg/cc) were randomized to *femhrt* 1/5 (1 **mg** norethindrone acetate/5 **mcg** ethinyl estradiol) or placebo, and 87% contributed data to the Intent-to-Treat analysis. All patients received 1000 mg calcium in divided doses. Vitamin D was not supplemented. *femhrt* 1/5 resulted in significant increases in BMD at each assessment. There was a significant decrease in BMD in the placebo group (see Figure 4).

FIGURE 4. Mean Percent Change (±SE) From Baseline in Lumbar Spine BMD at Months 12 and 24 (Intent-to-Treat Population)



* Mean percent changes in BMD statistically significantly more positive than mean percent changes in placebo group at each time point.

Information Regarding Lipid Effects

Patients enrolled in the 2-year osteoporosis and endometrial protection trial were evaluated for changes in lipid parameters after 24 months of therapy. All subjects were postmenopausal women at low risk for cardiovascular disease. Results for *femhrt* 1/5 and placebo arms are shown in Table 3.

TABLE 3. Mean % Change From Baseline Lipid Profile. Values After 24 Months of Treatment

	Placebo	*femhrt* 1/5 (mg NA/mcg EE)
Liquid Parameter	N = 129	N = 132
Total Cholesterol (mg/dL)	1.6	-7.0
HDL-C (mg/dL)	1.3	-6.7
LDL-C (mg/dL)	1.0	-7.5
Triglycerides (mg/dL)	19.1	12.1

NA = Norethindrone acetate. EE = Ethinyl estradiol.

INDICATIONS AND USAGE

femhrt 1/5 is indicated in women with an intact uterus for the:

1. Treatment of moderate to severe vasomotor symptoms associated with menopause.

2. Prevention of osteoporosis.

Since estrogen administration is associated with risks as well as benefits, selection of patients ideally should be based on prospective identification of risk factors for developing osteoporosis. Unfortunately, there is no certain way to identify those women who will develop osteoporotic fractures. Thus, patient selection must be individualized based on the balance of risks and benefits.

Estrogen replacement therapy reduces bone resorption and retards or halts postmenopausal bone loss. Case-control studies have shown an approximately 60% reduction in hip and wrist fractures in women whose estrogen replacement was begun within a few years of menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. Even when started as

late as 6 years after menopause, estrogen may prevent further loss of bone mass for as long as the treatment is continued. When estrogen therapy is discontinued, bone mass declines at a rate comparable to that in the immediate postmenopausal period. There is no evidence that estrogen replacement therapy restores bone mass to premenopausal levels.

Early menopause is one of the strongest predictors for the development of osteoporosis.

The mainstays of prevention and management of postmenopausal osteoporosis are estrogen, an adequate lifetime calcium intake, vitamin D and exercise. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. By comparison, premenopausal women require about 1000 mg/day and the average calcium intake in the USA is 400 to 600 mg/day. Therefore, when not contraindicated, calcium supplementation and adequate daily intake of vitamin D (400 IU) may be helpful.

CONTRAINDICATIONS

Progestogens/estrogens should not be used in individuals with any of the following conditions or circumstances:

1. Known or suspected pregnancy, including use for missed abortion or as a diagnostic test for pregnancy. Progestin or estrogen may cause fetal harm when administered to a pregnant woman.
2. Known or suspected cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Undiagnosed abnormal genital bleeding.
5. Active or past history of thrombophlebitis or thromboembolic disorders.
6. Known sensitivity to *femhrt* 1/5 or other estrogen and progestin containing products.

WARNINGS

1. Induction of Malignant Neoplasms

Endometrial Cancer

The reported endometrial cancer risk among users of unopposed estrogen is about 2- to 12-fold greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for use of 5 to 10 years or more, and this risk has been shown to persist for at least 15 years after cessation of estrogen treatment. Results from a 2-year clinical study of the effects of *femhrt* 1/5 on endometrial hyperplasia are shown in the **Clinical Studies** section of this label.

Clinical surveillance of all women taking progestin/estrogen combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that “natural” estrogens are more or less hazardous than “synthetic” estrogens at equivalent doses.

Breast Cancer

While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3-2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years.

The effect of added progestins on the risk of breast cancer is unknown.

2. Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogen has been reported.

3. Hypercalcemia

Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases (see **CONTRAINDICATIONS**). If this occurs, the drugs should be stopped and appropriate measures taken to reduce the serum calcium level.

4. Pregnancy

Use in pregnancy is not recommended (see **CONTRAINDICATIONS**).

5. Venous Thromboembolism

Five epidemiologic studies have found an increased risk of venous thromboembolism (VTE) in users of estrogen replacement therapy (ERT) who did not have predisposing conditions for VTE, such as a past history of cardiovascular disease or a recent history of pregnancy, surgery, trauma, or serious illness. The increased risk was found only in current ERT users; it did not persist in former users. The risk appeared to be higher in the first year of use and decreased thereafter. The findings were similar for ERT alone or with added progestin and pertain to commonly used oral and transdermal doses, with a possible dose-dependent effect on risk. The studies found the VTE risk to be about one case per 10,000 women per year among women not using ERT and without predisposing conditions. The risk in current ERT users was increased to 2-3 cases per 10,000 women per year.

6. Visual Disturbances

Medication should be discontinued pending examination if there is a sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

PRECAUTIONS

A. General

Based on experience with estrogens and/or progestins:

1. Cardiovascular Risk

A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.

In recent years many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy without cyclical progestins and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports:

(1) Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socioeconomic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Ongoing and future large-scale randomized trials may help to clarify the apparent benefit.

(2) Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri (see **PRECAUTIONS** and **WARNINGS**). While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL levels (see **Clinical Studies**).

(3) While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggests that progestins do not reduce, and may enhance the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see **WARNINGS**).

2. Elevated Blood Pressure

Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers.

Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. The data on the risk of estrogen use in postmenopausal women and the risk of stroke have not been considered conclusive. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.

3. Use in Hysterectomized Women

Existing data do not support the use of the combination of progestin and estrogen in postmenopausal women without a uterus.

4. Physical Examination

A complete medical and family history should be taken prior to the initiation of *femhrt* 1/5 and annually thereafter. These examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear.

5. Fluid Retention

Progestin/estrogen therapy may cause some degree of fluid retention. Conditions which might be exacerbated by this factor such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

6. Uterine Bleeding and Mastodynia

Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia. In cases of undiagnosed abnormal uterine bleeding, adequate diagnostic measures are indicated (see **WARNINGS**).

7. Impaired Liver Function

Estrogens and progestins may be poorly metabolized in patients with impaired liver function. If needed, therapy should be administered with caution.

8. Pathology Specimens

The pathologist should be advised of progestin/estrogen therapy when relevant specimens are submitted.

9. Hypercoagulability

Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have changes in coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (of primarily conjugated estrogen users) report no such increase. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease, therefore, *femhrt* 1/5 is contraindicated in such women.

10. Familial Hyperlipoproteinemia

Estrogen therapy may be associated with massive elevations of plasma trigylcerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

11. Depression

Patients who have a history of depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

12. Impaired Glucose Tolerance

Diabetic patients should be carefully observed while receiving progestin/estrogen therapy. The effects of *femhrt* 1/5 on glucose tolerance have not been studied.

13. Lipoprotein Metabolism

(See **Clinical Studies**.)

B. Information for Patients

See text of Patient Package Insert which appears after the **HOW SUPPLIED** section.

C. Drug/Laboratory Test Interactions

The following drug/laboratory interactions have been observed with estrogen therapy, and/or *femhrt* 1/5:

1. In a 12-week study, *femhrt* 1/5 decreased Factor VII and plasminogen activator inhibitor-1 from baseline in a dose-related manner, but remained within the laboratory reference range for postmenopausal women. Mean levels of fibrinogen and partial thromboplastin time did not change from baseline for *femhrt* 1/5.

2. Estrogen therapy may increase thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone (T4) as measured by protein-bound iodine (PBI), T4 levels (by column or radioimmunoassay), or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered.

3. Estrogen therapy may elevate other binding proteins in serum, ie, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

femhrt 1/5 was associated with a SHBG increase of 22%.

4. Estrogen therapy increases plasma HDL and HDL-2 subfraction concentrations, reduces LDL cholesterol concentration and increases triglyceride levels. (For effects during *femhrt* 1/5 treatment, see **Clinical Studies**.)

5. Estrogen therapy is associated with impaired glucose tolerance.

6. Estrogen therapy reduces response to metyrapone test.

7. Estrogen therapy reduces serum folate concentration.

D. Drug/Drug Interactions

No drug-drug interaction studies have been conducted with *femhrt* 1/5.

The following section contains information on drug interactions with ethinyl estradiol-containing products (specifically, oral contraceptives) that have been reported in the public literature. It is unknown whether such interactions occur with *femhrt* 1/5 or drug products containing other types of estrogens.

The Effects of Other Drugs on Ethinyl Estradiol

The metabolism of ethinyl estradiol is increased by rifampin and anticonvulsants such as phenobarbital, phenytoin, and carbamazepine. Coadministration of troglitazone and certain ethinyl estradiol containing drug products (eg, oral contraceptives containing ethinyl estradiol) reduce the plasma concentrations of ethinyl estradiol by 30 percent.

Ascorbic acid and acetaminophen may increase AUC and/or plasma concentrations of ethinyl estradiol. Coadministration of atorvastatin and certain ethinyl-estradiol containing drug products (eg, oral contraceptives containing ethinyl estradiol) increase AUC values for ethinyl estradiol by 20 percent.

Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

The Effect of Ethinyl Estradiol on Other Drugs

Drug products containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of certain drugs containing ethinyl estradiol (eg, oral contraceptives containing ethinyl estradiol). In addition, drugs containing ethinyl estradiol may induce the conjugation of other compounds.

Decreased plasma concentrations of acetaminophen and increased clearance of temazapam, salicylic acid, morphine, and clofibric acid have been noted when these drugs were administered with certain ethinyl-estradiol containing drug products (eg, oral contraceptives containing ethinyl estradiol).

E. Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of natural and synthetic estrogens in certain animal species increase the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver (see **CONTRAINDICATIONS** and **WARNINGS**).

F. Pregnancy Category X

Estrogens/progestins should not be used during pregnancy (see **CONTRAINDICATIONS** and **WARNINGS**).

G. Nursing Mothers

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of drug have been identified in the milk of mothers receiving progestational drugs. The effect of this on the nursing infant has not been determined.

ADVERSE REACTIONS

Adverse events reported in controlled clinical studies of *femhrt* 1/5 are shown in Table 4 below.

TABLE 4. All Treatment-Emergent Adverse Events Reported at a Frequency of >5% of Patients with *femhrt* 1/5

	% of Patients	
BODY SYSTEM/	Placebo	*femhrt* 1/5
Adverse Event	N = 247	N = 258
BODY AS A WHOLE	40.1	39.5
Headache	14.6	18.2
Back Pain	5.3	4.7
Pain	4.5	3.9
Viral Infection	7.7	7.0
Edema-Generalized	4.9	4.7
DIGESTIVE SYSTEM	24.4	33.0
Nausea and/or Vomiting	5.3	7.4
Abdominal Pain	4.5	8.1
Constipation	4.0	3.1
MUSCULOSKELETAL SYSTEM	21.7	20.4
Arthralgia	6.9	5.8
Myalgia	8.5	7.8
PSYCHOBIOLOGIC FUNCTION	8.3	14.1
Nervousness	1.6	5.4
Depression	3.6	5.8
RESPIRATORY SYSTEM	37.2	35.6
Rhinitis	15.4	15.1
Sinusitis	9.7	8.1
Upper Respiratory Infection	4.5	3.9
UROGENITAL SYSTEM	25.0	40.8
Breast Pain	5.3	8.1
Urinary Tract Infection	3.2	6.2
Vaginitis	4.9	5.4

The following adverse events have been reported with estrogen and/or progestin therapy:

Genitourinary system: changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, increase in size of uterine leiomyomata, vaginal candidiasis, changes in amount of cervical secretion, premenstrual-like syndrome, cystitis-like syndrome.

Breasts: tenderness, enlargement, fibrocystic disease of the breast.

Gastrointestinal: cholestatic jaundice, pancreatitis, flatulence, bloating, abdominal cramps.

Skin: chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, itching, skin rash and pruritus.

CNS: headache, migraine, dizziness, chorea, insomnia.

Cardiovascular: changes in blood pressure, cerebrovascular accidents, deep venous thrombosis, and pulmonary embolism.

Eyes: intolerance to contact lenses, sudden partial or complete loss of vision, proptosis, diplopia, otosclerosis.

Miscellaneous: increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, changes in libido, fatigue, allergic or anaphylactoid reactions, leiomyoma, fibromyoma of the uterus, endometriosis.

OVERDOSAGE

ACUTE OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of progestin/estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur.

DOSAGE AND ADMINISTRATION

femhrt 1/5 therapy consists of a single tablet taken once daily.

1. For the Treatment of Vasomotor Symptoms

femhrt 1/5 should be given once daily for the treatment of moderate to severe vasomotor symptoms associated with the menopause. Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary.

2. Prevention of Osteoporosis

femhrt 1/5 should be given once daily to prevent postmenopausal osteoporosis (see **Clinical Studies: Effect on Bone Mineral Density**). Response to therapy can be assessed by measurement of bone mineral density.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer, and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring vaginal bleeding. Patients should be evaluated at least annually for breast abnormalities and more often if there are any symptoms.

HOW SUPPLIED

femhrt 1/5 tablets are white and available in the following strength and package sizes:

N 0071-0144-23	Bottle of 90 D-shaped tablets with 1 **mg** norethindrone acetate and 5 **mcg** ethinyl estradiol
N 0071-0144-45	Blister card of 28 D-shaped tablets with 1 **mg** norethindrone acetate and 5 **mcg** ethinyl estradiol

℞ **only**

Keep this drug and all drugs out of the reach of children.

Store at 25˚C (77˚F); excursions permitted to 15 - 30˚C (59 - 86˚F) [see USP Controlled Room Temperature].

INFORMATION FOR THE PATIENT

What is *femhrt* 1/5?

Your healthcare provider has prescribed *femhrt* 1/5, a combination of two hormones, a progestin (1 mg norethindrone acetate) and an estrogen (5 mcg ethinyl estradiol) intended for use once a day. This insert describes the major benefits and risks of your treatment, as well as how and when treatment may be taken. If you have any questions, please contact your physician, nurse or pharmacist.

***femhrt* 1/5 is approved for use in the following ways:**

- **To reduce moderate to severe menopausal symptoms.** Estrogens are hormones produced by the ovaries of menstruating women. When a woman is between

the ages of 45 and 55, the ovaries normally stop making estrogens. This drop in body estrogen levels causes the "change of life" or menopause, the end of monthly menstrual periods.

When estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild; in others they can be severe. These symptoms may last only a few months or longer. Taking *femhrt* 1/5 can help reduce these symptoms. If you are not taking hormones for other reasons, such as the prevention of osteoporosis, you should take *femhrt* 1/5 only as long as you need it for relief from your menopausal symptoms.

- **To prevent thinning bones (osteoporosis).** Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists, and hips may be affected by osteoporosis. *femhrt* 1/5 may be used as part of a program including weight-bearing exercise, such as walking or running, and calcium supplements.

  Women likely to develop osteoporosis often have the following characteristics: white or Asian race, slim, cigarette smokers, and a family history of osteoporosis in a mother, sister, or aunt. Women who have menopause at an earlier age, either naturally or because their ovaries were removed during an operation, are more likely to develop osteoporosis than women whose menopause happens later in life.

Who should not take *femhrt* 1/5?

femhrt 1/5 should not be taken in the following situations:

- **During pregnancy.** If you think you may be pregnant, do not take *femhrt* 1/5. Taking estrogens while you are pregnant may cause your unborn child to have birth defects. Do not take *femhrt* 1/5 to prevent miscarriage.
- **If you have unusual vaginal bleeding that has not been checked by your health-care provider.** Unusual vaginal bleeding can be a warning sign of a serious condition, including cancer of the uterus, especially if bleeding happens after menopause. Your doctor must find out the cause of the bleeding to recommend the right treatment.
- **If you have had certain cancers.** Estrogens increase the risk of certain types of cancers, including cancer of the breast and uterus. If you have had cancer, talk with your doctor about whether you should take *femhrt* 1/5.
- **If you have any circulation problems.** Generally, estrogens should not be taken if you have ever had a blood-clotting condition or other circulatory problem. In special situations, some doctors may decide that estrogen therapy is so necessary that the risks of taking *femhrt* 1/5 are acceptable (see “What are the possible risks and side effects of *femhrt* 1/5?”).
- **After childbirth or when breast-feeding a baby.** *femhrt* 1/5 should not be used to try to stop the breasts from filling with milk after a baby is born. Taking *femhrt* 1/5 may increase your risk of developing blood clots (see “What are the possible risks and side effects of *femhrt* 1/5?”).
- **If you have had a hysterectomy (uterus removed).** *femhrt* 1/5 contains a progestin to decrease the risk of developing endometrial hyperplasia (an overgrowth of the lining of the uterus that may lead to cancer). If you do not have a uterus, you do not need a progestin, and you should not take *femhrt* 1/5.

How should I take *femhrt* 1/5?

Take your *femhrt* 1/5 pill once a day at about the same time each day. If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take only your next regularly scheduled dose. Do not take two doses at the same time.

The length of treatment with estrogens varies from woman to woman. You and your healthcare provider should reevaluate every 3 to 6 months whether or not you still need *femhrt* 1/5 to control your hot flashes.

What are the possible risks and side effects of *femhrt* 1/5?

- **Cancer of the uterus.** *femhrt* 1/5 has estrogen and progestin in it. If you take any drug that contains estrogen, including *femhrt* 1/5, you should see your doctor for regular check-ups and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of a serious condition, including cancer of the uterus. Your doctor should identify the cause of any unusual vaginal bleeding.

  The risk of cancer of the uterus increases when estrogens are used without a progestin. The risk also increases the longer estrogens are taken and the larger the doses. You are more likely to get cancer of the uterus if you are overweight, diabetic, or have high blood pressure. *femhrt* 1/5, which contains a progestin, reduces the estrogen-related risk of getting a condition of the uterine lining called endometrial hyperplasia. This condition may lead to cancer of the uterus (see "Other Information").
- **Cancer of the breast.** Most studies have not shown a higher risk of breast cancer in women who have used estrogens. However, some studies report that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for longer time periods, especially more than 10 years, or who used high doses for a shorter time period. The effects of added progestin on the risk of breast cancer are unknown. You should have regular breast examinations by a health professional and examine your own breasts monthly. Ask your health-care provider to show you how to do a breast exam yourself. If you are over 50 years of age, you should have a mammogram every year.
- **Gallbladder disease.** Women who use estrogens after menopause are more likely to develop gallbladder disease that leads to surgery than women who do not use estrogens.
- **Abnormal blood clotting.** Taking estrogens may cause changes in your blood clotting system that allow the blood to clot more easily. If blood clots form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting off blood to the heart), or a pulmonary embolus (by cutting off blood supply to the lungs). Any of these conditions may cause death or serious long-term disability.
- **Vaginal bleeding.** With *femhrt* 1/5, menstrual-like vaginal bleeding may occur. If bleeding occurs, it is frequently light spotting or bleeding, but it may be moderate or heavy. If you experience vaginal bleeding while taking *femhrt* 1/5, discuss your bleeding pattern with your healthcare provider.

In addition to the risks and side effects just listed, patients taking estrogen or progestin have reported the following side effects:

- nausea and vomiting
- breast tenderness or enlargement

- headache
- retention of extra fluid (edema), which may make some conditions worse, such as asthma, epilepsy, migraine, heart disease, or kidney disease
- runny nose
- abdominal pain
- enlargement of non-cancerous tumors (fibroids) of the uterus
- spotty darkening of the skin, particularly on the face; reddening of the skin; skin rashes

How can I reduce the risks associated with taking *femhrt* 1/5?

If you take *femhrt* 1/5, you can reduce your risks by carefully monitoring your treatment.

- **See your healthcare provider regularly.** While you take *femhrt* 1/5, see your doctor at least once a year for a checkup. If you develop vaginal bleeding while taking *femhrt* 1/5, you might need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need more frequent breast examinations.
- **Reassess your need for treatment.** Every 3-6 months, you and your doctor should discuss whether or not you still need *femhrt* 1/5 for control of your hot flashes.
- **Be alert for signs of trouble.** If any of the following warning signs (or any other unusual symptoms) happen while you are taking *femhrt* 1/5, call your doctor right away:
  - pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clots in the legs, heart, or lungs)
  - severe headache or vomiting, dizziness, faintness, or changes in vision or speech, weakness or numbness of an arm or leg (possible clots in the brain or eye)
  - breast lumps (possible breast cancer)
  - yellowing of the skin or whites of the eyes (possible liver problems)
  - pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

Other Information

- Discuss carefully with your doctor or healthcare provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.
- If you take calcium supplements as part of your treatment to help prevent osteoporosis, ask your doctor about the amounts recommended. A daily intake of 1500 mg of calcium is often recommended for postmenopausal women. Vitamin D (400 IU daily) may help your body use more of the calcium.
- Taking estrogens with progestins may have unhealthy effects on blood sugar, which might make a diabetic condition worse.
- Your doctor has prescribed this drug for you and you alone. Do not give your *femhrt* 1/5 to anyone else. Do not take *femhrt* 1/5 for conditions for which it was not prescribed.
- Keep all drugs out of the reach of children. In case of overdose, call your doctor, hospital, or poison control center right away.

This leaflet provides the most important information about *femhrt* 1/5. If you want more information, ask your doctor or pharmacist for the professional labeling. The professional labeling is published in a book called "The Physicians' Desk Reference" or PDR, available in bookstores and public libraries.

Revised February 2000
Manufactured by:
DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

Distributed by:
PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

0132G031